Healthcare Professional Educational Pack for

VIBATIV® ▼ (telavancin)

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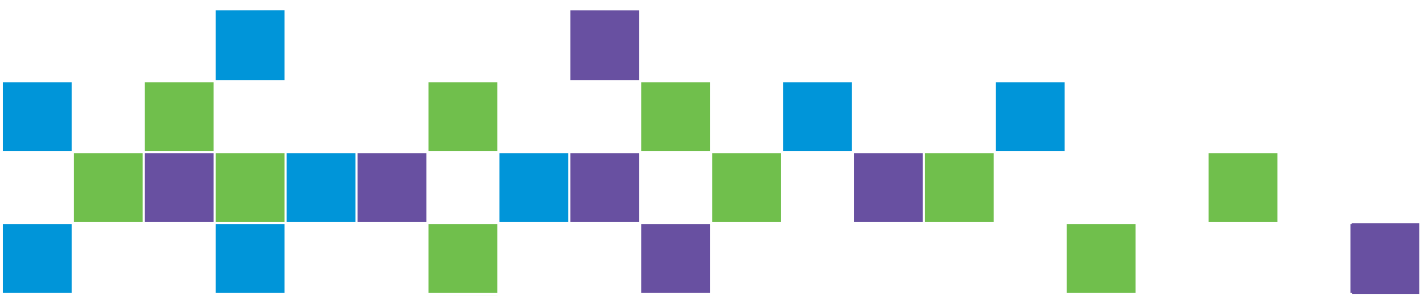

Healthcare Professional Educational Pack for Vibativ®

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VIBATIV® ▼ (telavancin)

Healthcare Professional's Guide

20 January 2014

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Introduction

As the marketing authorisation holder, Clinigen has to fulfill certain post-approval obligations; this education guide is a mandatory condition of the marketing authorisation. It is to inform you of important safety aspects associated with the use of Vibativ® and how to manage these in order to minimize the risk to the patient.

About Vibativ® / Therapeutic indications

Vibativ® is a semisynthetic lipoglycopeptide antibacterial agent and is indicated for the treatment of adults with nosocomial pneumonia (NP) including ventilator associated pneumonia (VAP), known or suspected to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Vibativ® should be used only in situations where other alternative treatments are not appropriate or have failed (see Summary of Product Characteristics, sections 4.3, 4.4 and 5.1) [1].

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Antimicrobial spectrum of activity for Vibativ®

Vibativ® is active against

• *Staphylococcus aureus* (including methicillin-resistant strains) with an MIC ≤1 mcg/ml

Vibativ® is not active against Gram-negative bacteria.

Important risks of Vibativ®

The following important risks that arise with the use of Vibativ® require special attention and patient monitoring. Further details on these and other risks can be found also in the Summary of Product Characteristics in sections 4.3 – 4.9.

Off label use

The benefit/risk balance of Vibativ® in treatment of complicated skin and soft tissue infections was assessed as negative by the CHMP, the EU committee providing scientific opinions on marketing authorisation applications for medicinal products. Vibativ® should not be used in this or other non-approved indications.

Nephrotoxicity /Renal insufficiency

In the clinical studies, patients with preexisting acute renal failure receiving Vibativ® had an increased risk of death compared with those receiving vancomycin. All-cause mortality was 32/73 (44%) in the Vibativ® group and 16/64 (25%) in the vancomycin group. In patients without acute renal failure at baseline it was 118/678 (17%) and 124/688 (18%), respectively. Therefore the use of Vibativ® is contraindicated in patients with preexisting acute renal failure and in patients with severe renal impairment (CrCl <30 ml/min, including patients undergoing hemodialysis). Dose adjustment is needed for patients with creatinine clearance of 30 to 50 ml/min. *See table below.*

In pooled clinical studies (nosocomial pneumonia and complicated skin and soft tissue infection), renal adverse reactions were reported more frequently in patients receiving Vibativ® compared with vancomycin (3.8% vs. 2.2%, respectively).

Patient monitoring in renal function

• Renal function should be monitored in all patients receiving Vibativ®

• Renal function (serum creatinine and urinary output for oliguria/anuria) should be monitored daily for at least the first 3 to 5 days of therapy and every 48 to 72 hours thereafter in all patients receiving Vibativ®.

• Initial dose and dosage adjustments during treatment should be made based on calculated or measured creatinine clearance according to the dosing regimen in section 4.2 of the SmPC and

the table below. If renal function markedly decreases during treatment, the benefit of continuing Vibativ® should be assessed.
• Caution should be used when prescribing Vibativ® to patients receiving concomitant nephrotoxic medication, those with preexisting renal disease or with co-morbidity known to predispose to kidney dysfunction (e.g., diabetes mellitus, congestive heart failure, hypertension).

Creatinine clearance* (mL/min)	Dosage regimen
>50	10 mg/kg every 24 hours
30–50	7.5 mg/kg every 24 hours
<30, including patients undergoing haemodialysis	Contraindicated
*As calculated using the Cockcroft-Gault formula	

Potential Risk of Teratogenicity / Checklist for pregnancy status

The use of Vibativ® is contraindicated in pregnancy.

The pregnancy status of women of childbearing potential should be established prior to dosing with Vibativ®. Women of childbearing potential should use effective contraception during Vibativ® therapy.

Embryo-fetal development studies in animals indicate that Vibativ® has teratogenic potential which manifests primarily as skeletal findings including limb malformations. The potential risk for humans is unknown. Therefore, the pregnancy status of women of childbearing potential should be established prior to dosing with Vibativ® (serum hCG test). A prescriber checklist is available as a peel-off sticker shipped with the product vial to ensure that Vibativ® is not administered before the patient's negative pregnancy status is confirmed.

The checked sticker should be fixed to the patient chart prior to administration of Vibativ®.
Where clinically appropriate, women of childbearing potential must be advised to use effective contraception during Vibativ® therapy.

Patients should be instructed to notify their prescribing physician/healthcare provider if they become pregnant while taking Vibativ®. There is a pregnancy registry for all women who are exposed to Vibativ® during pregnancy. For further information and enrolment, please call **+44 (0) 1748 828375** or email **clinigenEU@professionalinformation.co.uk**
Information can also be found at **www.vibativ.eu**

QTc prolongation

Caution is warranted when using Vibativ® to treat patients taking medicinal products known to prolong the QT interval. Subjects with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy were not included in clinical trials of Vibativ®.

Other significant risks

Infusion related reactions

Rapid intravenous infusions with glycopeptide antibiotics class have been associated with red man syndrome-like reactions. Stopping or slowing the infusion may result in cessation of these reactions. To minimize the likelihood of infusion related reactions, the daily dose should be administered over a one-hour period.

Ototoxicity

Ototoxicity has not been studied in patients treated with Vibativ®. Pharmacological class-related ototoxicity cannot be excluded in these patients.
• Patients who develop signs and symptoms of impaired hearing or disorders of the inner ear

during treatment with Vibativ® should be carefully evaluated and monitored.
• Patients receiving Vibativ® in conjunction with or sequentially with other medication with known ototoxic potential should be carefully monitored and the benefit of Vibativ® evaluated if hearing deteriorates.

Interference with Clinical Tests

Coagulation testing

Although Vibativ® does not interfere with coagulation, it can interfere with certain tests used to monitor coagulation *(see table below)*, when tests are conducted using samples drawn between 0 to 18 hours after Vibativ® administration to the patient. The recommendation is that blood samples for coagulation tests should be collected as closely as possible prior to a patient's next dose of Vibativ® or consideration given to using a test unaffected by Vibativ®[2].

Coagulation tests affected by VIBATIV	Coagulation tests unaffected by VIBATIV
International normalised ratio	Whole blood (Lee-White) clotting time
Activated partial thromboplastin time	Ex vivo platelet aggregation
Activated clotting time	Chromogenic factor Xa assay
Coagulation based factor Xa tests	Functional (chromogenic) factor X assay
	Bleeding time
	D-dimer
	Fibrin degradation products

Urinary protein excretion

Vibativ® interferes with urine dipstick and quantitative dye methods of assessing urinary protein excretion. Microalbumin immunoassays are not affected and can be used instead.

Useful contacts

Further information about Vibativ® can be obtained by visiting **www.vibativ.eu** or via the approved product information available at **www.ema.europa.eu**

Information on the pregnancy registry can also be obtained by calling Professional Information on **+44 (0) 1748 828375** or email **clinigenEU@professionalinformation.co.uk**

Call for reporting suspected adverse reactions

Suspected adverse reactions should be reported to Clinigen by fax on **+44 (0) 1442 500615** or email **pharmacovigilance@Aptivsolutions.com** and to the local authority:

Adverse events and medication errors should be reported to the Medicines Authority by mail to;
ADR Reporting
The Medicines Authority, Post-Licensing Directorate
203 Level 3, Rue D'Argens
Gzira GZR 1368, Malta

Online at **www.medicinesauthority.gov.mt/adrportal**

Pregnancies occurring after treatment with Vibativ® should be reported by calling **+44 (0) 1748 828375** or email **clinigenEU@professionalinformation.co.uk**

Further information can also be found at **www.vibativ.eu**

References

1) SmPC Vibativ®. The valid product information for Vibativ can be downloaded from the website of EMA (European Medicines Agency): **www.ema.europa.eu**

2) Ero, M.P., Harvey, N.R., Harbert, J.L., Janc, J.W., Chin, K.H., Barriere, S.L.; Impact of telavancin on prothrombin time and activated partial thromboplastin time as determined using point-of-care coagulometers. Journal of Thrombosis and Thrombolysis, 2013 Oct

SUMMARY OF PRODUCT CHARACTERISTICS

VIBATIV 250 mg/750 mg, powder for concentrate for solution for infusion.

Telavancin

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

VIBATIV 250 mg / 750 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250 mg / 750 mg telavancin (as hydrochloride).

After reconstitution, each ml contains 15 mg of telavancin.

Excipients:

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

A white to pale pink, whole or fragmented cake

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VIBATIV is indicated for the treatment of adults with nosocomial pneumonia (NP) including ventilator associated pneumonia, known or suspected to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

VIBATIV should be used only in situations where it is known or suspected that other alternatives are not suitable (see sections 4.3, 4.4, 4.8 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults

The recommended dosage regimen is 10 mg/kg, once every 24 hours, for 7 to 21 days.

Special populations

Paediatric patients

The safety and efficacy of VIBATIV in children aged below 18 years have not yet been established. No data are available.

Dosage in patients with renal impairment

Patients with renal impairment should receive an initial dose according to calculated or measured creatinine clearance as presented in the table below. During treatment dose adjustments according to the table should be made based on calculated or measured creatinine clearance in patients with clinically relevant changes in renal function.

Creatinine clearance* (ml/min)	Dosage regimen
>50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours

*As calculated using the Cockcroft-Gault formula

The use in patients with acute renal failure or creatinine clearance (CrCl) <30 ml/min including patients undergoing haemodialysis is contraindicated (see section 4.3).

Dosage in patients with hepatic impairment

Mild to moderate degrees of hepatic impairment (Child-Pugh class B) (see section 5.2) did not result in a relevant change in pharmacokinetics of telavancin. Therefore, no dose adjustment is necessary when administering telavancin to subjects with mild or moderate degrees of hepatic impairment. No data are available in subjects with severe hepatic impairment (Child-Pugh class C). Therefore, caution should be exercised if telavancin is given to subjects with severe hepatic impairment.

Obese patients

Obese patients should receive a telavancin dose in accordance with their bodyweight and renal function (see section 4.3 and 5.2).

Elderly patients

Elderly patients should receive a telavancin dose in accordance with their bodyweight and renal function (see section 4.3 and 5.2).

Method of administration

VIBATIV must be reconstituted and then further diluted prior to administration by intravenous infusion through a dedicated line or through a Y-site over a 60 minute period. Bolus injections must not be administered. For instructions on reconstitution and dilution, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with severe renal impairment, i.e. creatinine clearance (CrCl) <30 ml/min, including patients undergoing haemodialysis (see section 4.4).
Acute renal failure (see section 4.4).
Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Renal impairment
In the clinical studies, patients with pre existing acute renal failure receiving telavancin had an increased risk of mortality. All-cause mortality was 32/73 (44%) in the telavancin group and 16/64 (25%) in the vancomycin group, whereas in patients without acute renal failure at baseline it was 118/678 (17%) and 124/688 (18%), respectively. Therefore the use of telavancin in patients with pre-existing acute renal failure and in patients with severe renal impairment is contraindicated (see section 4.3).

Renal adverse reactions
In the pooled clinical studies (NP and complicated skin and soft tissue infection (cSSTI)), renal adverse reactions were reported more frequently in patients receiving VIBATIV compared with vancomycin (3.8% vs. 2.2%, respectively). Renal function (serum creatinine and urinary output for oliguria/anuria) should be monitored daily for at least the first 3 to 5 days of therapy and every 48 to 72 hours thereafter in all patients receiving VIBATIV. Initial dose and dosage adjustments during treatment should be made based on calculated or measured creatinine clearance according to the dosing regimen in section 4.2. If renal function markedly decreases during treatment, the benefit of continuing VIBATIV should be assessed.

Other factors that may increase the risk of nephrotoxicity
Caution should be used when prescribing VIBATIV to patients receiving concomitant nephrotoxic medicines, those with pre existing renal disease or with co-morbidity known to predispose to kidney dysfunction (e.g. diabetes mellitus, congestive heart failure, hypertension).

Infusion related reactions
Rapid intravenous infusions of antimicrobial agents of the class of glycopeptides have been associated with red man syndrome-like reactions, including flushing of the upper body, urticaria, pruritus or rash (see section 4.8). Stopping or slowing the infusion may result in cessation of these reactions. Infusion related reactions can be limited if the daily dose is infused over a 1 hour period.

Hypersensitivity
Hypersensitivity reactions, including anaphylaxis, have been reported with the use of antibacterial agents, including telavancin, and may be life-threatening. If an allergic reaction to telavancin occurs, discontinue the drug and institute appropriate therapy. Cross hypersensitivity reactions, including anaphylaxis, have been reported in patients with a history of vancomycin allergy. Caution should be exercised when prescribing telavancin to patients with a prior history of hypersensitivity reaction to vancomycin. If an allergic reaction to telavancin occurs, discontinue the drug and institute appropriate therapy.

QTc prolongation
A clinical QTc study with telavancin doses of 7.5 and 15 mg/kg versus vehicle and an active comparator (400 mg moxifloxacin) showed that once daily dosing for 3 days resulted in a mean vehicle corrected increase in QTcF by 4.1 and 4.5 millisecond, respectively, compared to a 9.2 millisecond increase observed with the comparator.

Caution is warranted when using telavancin to treat patients taking medicinal products known to prolong the QT interval. In addition, caution is warranted when using telavancin to treat patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy. Patients with these conditions were not included in clinical trials of telavancin.

Ototoxicity
As with other glycopeptides, ototoxicity (deafness and tinnitus) has been reported in patients treated with telavancin (see section 4.8). Patients who develop signs and symptoms of impaired hearing or disorders of the inner ear during treatment with telavancin should be carefully evaluated and monitored (see section 4.8). Patients receiving telavancin in conjunction with or sequentially with other medication with known ototoxic potential should be carefully monitored and the benefit of telavancin evaluated if hearing deteriorates.

Superinfection
The use of antibiotics may promote the overgrowth of non-susceptible micro-organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Antibiotic-associated colitis and pseudomembranous colitis
Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial agents, including telavancin (see section 4.8), and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or shortly following treatment.

Concomitant antibiotic coverage
Telavancin is active against Gram-positive bacteria only (see section 5.1 for information on the antimicrobial spectrum). In mixed infections where Gram-negative and/or certain types of anaerobic bacteria are suspected, VIBATIV should be co-administered with appropriate antibacterial agent(s).

Specific patient groups
The nosocomial pneumonia (NP) studies excluded known or suspected pulmonary disease like granulomatous diseases, lung cancer, or other malignancy metastatic to the lungs; cystic fibrosis or active tuberculosis; *Legionella pneumophila* pneumonia; meningitis, endocarditis, or osteomyelitis; refractory shock defined as supine systolic blood pressure <90 mm Hg for >2 hours with evidence of hypoperfusion or requirement for high-dose sympathomimetic agents. Also patients with baseline QTc >500 msec, congenital long QT syndrome, uncompensated heart failure, or abnormal K^+ or Mg^{2+} blood levels that could not be corrected, severely neutropenic (absolute neutrophil count <500/mm^3) or anticipated to develop severe neutropenia due to prior or planned chemotherapy, or who had HIV with CD4 count <100/mm^3 during the last 6 months were excluded.

4.5 Interaction with other medicinal products and other forms of interaction
In studies in healthy subjects, the pharmacokinetics of telavancin were not significantly altered by simultaneous administration of aztreonam or piperacillin-tazobactam. Also, the pharmacokinetics of aztreonam or piperacillin tazobactam were not altered by telavancin. Based on their pharmacokinetic properties, no interaction is expected with other beta-lactams, clindamycin, metronidazole, or fluoroquinolones.

It was demonstrated in a clinical study with intravenous midazolam that multiple doses of telavancin had no effect on the pharmacokinetics of midazolam, which is a sensitive substrate for CYP3A4. *In vitro* experiments indicate that telavancin will not affect the clearance of medicinal products metabolised by CYP isoforms 1A2, 2C9, 2C19 and 2D6. Since telavancin is primarily excreted unchanged by renal clearance and multiple CYP enzymes are able to metabolise telavancin, no relevant interactions are expected with inhibitors or inducers of the CYP450 system.

Although telavancin does not interfere with coagulation, it interfered with certain tests used to monitor coagulation (see below), when tests are conducted using samples drawn between 0 to 18 hours after telavancin administration to patients being treated once every 24 hours. Blood samples for coagulation tests should be collected as closely as possible prior to a patient's next dose of telavancin or consideration given to using a test unaffected by VIBATIV.

Coagulation tests affected by telavancin	Coagulation tests unaffected by telavancin
International normalised ratio	Whole blood (Lee-White) clotting time
Activated partial thromboplastin time	Ex vivo platelet aggregation
Activated clotting time	Chromogenic factor Xa assay
Coagulation based factor Xa tests	Functional (chromogenic) factor X assay
	Bleeding time
	D-dimer
	Fibrin degradation products

No evidence of increased bleeding risk has been observed in clinical trials with telavancin. Telavancin has no effect on platelet aggregation. Furthermore, no evidence of hypercoagulability has been seen, as healthy subjects receiving telavancin have normal levels of D-dimer and fibrin degradation products.

Telavancin interferes with urine qualitative dipstick protein assays, as well as quantitative dye methods (e.g. pyrogallol red molybdate). Microalbumin assays based on immunoassay utilizing nephelometric (turbidity) detection are not affected and can be used to monitor urinary protein excretion during telavancin treatment. For routine monitoring of renal function it is recommended to use serum creatinine concentration or estimated creatinine clearance.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of VIBATIV is contraindicated during pregnancy (see section 4.3).
There is no human experience with VIBATIV. Studies in animals have shown reproductive toxicity (see section 5.3).
The pregnancy status of women of childbearing potential has to be established prior to dosing with VIBATIV. Women of childbearing potential have to use effective contraception during treatment.

Breastfeeding
It is unknown whether telavancin is excreted in human breast milk. The excretion of telavancin in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with telavancin should be made taking into account the benefit of breastfeeding to the child and the benefit of telavancin therapy to the woman.

Fertility
Telavancin has been shown to affect sperm quantity and quality of male rats (see section 5.3) although no effect on fertility, mating, or early embryogenesis has been reported. The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Dizziness, somnolence, confusion and blurred vision may occur and these may have an influence on the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects
In phase 3 clinical trials involving 1680 patients (751 and 929, NP and cSSTI, respectively) who received telavancin at a daily dose of 10 mg/kg, adverse reactions were reported in 47.3% of patients. Treatment was discontinued due to adverse reactions in 5.0% of patients who received telavancin.

The most commonly reported related adverse reactions (occurring in >1% of patients) were: fungal infection, insomnia, dysgeusia, headache, dizziness, nausea, constipation, diarrhoea, vomiting,

alanine aminotransferase increased, aspartate aminotransferase increased, pruritus, rash, renal failure acute, blood creatinine increased, urine abnormality (foamy urine), fatigue and chills.

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Common:	fungal infection
Uncommon:	clostridium colitis, urinary tract infection

Blood and lymphatic system disorders

Uncommon:	anaemia, leukopenia, thrombocythaemia, thrombocytopenia, eosinophil count increased, neutrophil count increased

Immune system disorders

Uncommon:	hypersensitivity
Not known*	anaphylaxis

Metabolism and nutrition disorders

Uncommon:	decreased appetite, hyperglycaemia, hyperkalaemia, hypoglycaemia, hypokalaemia, hypomagnesaemia

Psychiatric disorders

Common:	insomnia
Uncommon:	agitation, anxiety, confusional state, depression

Nervous system disorders

Very common:	dysgeusia
Common:	headache, dizziness
Uncommon:	ageusia, migraine, paraesthesia, parosmia, somnolence, tremor

Eye disorders

Uncommon:	eye irritation, blurred vision

Ear and labyrinth disorders

Uncommon:	tinnitus
Rare:	deafness

Cardiac disorders

Uncommon:	angina pectoris, atrial fibrillation, bradycardia, cardiac failure congestive, electrocardiogram QT corrected interval prolonged, palpitations, sinus tachycardia, supraventricular extrasystoles, ventricular extrasystoles

Vascular disorders

Uncommon:	flushing, hypertension, hypotension, phlebitis

Respiratory, thoracic and mediastinal disorders

Uncommon:	dyspnoea, hiccups, nasal congestion, pharyngolaryngeal pain

Gastrointestinal disorders

Very common:	nausea
Common:	constipation, diarrhoea, vomiting
Uncommon:	abdominal pain, dry mouth, dyspepsia, flatulence, hypoaesthesia oral

Hepatobiliary disorders

Common:	alanine aminotransferase increased, aspartate aminotransferase increased
Uncommon:	hepatitis

Skin and subcutaneous tissue disorders

Common:	pruritus, rash
Uncommon:	erythema, face oedema, hyperhidrosis, urticaria

Musculoskeletal and connective tissue disorders

Uncommon:	arthralgia, back pain, muscle cramp, myalgia

Renal and urinary disorders

Common:	renal failure acute, blood creatinine increased, foamy urine (lower level term)
Uncommon:	blood urea increased, dysuria, haematuria, microalbuminuria, oliguria, pollakiuria, renal impairment, urine odour abnormal

General disorders and administration site conditions

Common:	fatigue, chills
Uncommon:	asthenia, infusion site reactions, malaise, non-cardiac chest pain, peripheral oedema, pain, pyrexia, Red Man syndrome

Investigations

Uncommon:	international normalised ratio increased

* Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

ADR Reporting
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

4.9 Overdose

In healthy volunteers who received a dose of 15 mg/kg, a higher incidence of adverse reactions to telavancin was seen: dysgeusia, nausea, vomiting, injection site erythema, headache, macular rash, and red man syndrome.

In the event of overdose, telavancin should be discontinued and supportive care is advised with maintenance of glomerular filtration and careful monitoring of renal function. Following administration of a single dose of telavancin 7.5 mg/kg to subjects with end-stage renal disease, approximately 5.9% of the administered dose of telavancin was recovered in the dialysate following 4 hours of haemodialysis. However, no information is available on the use of haemodialysis to treat an overdose.

The clearance of telavancin by continuous venovenous haemofiltration (CVVH) was evaluated in an *in vitro* study. Telavancin was cleared by CVVH and the clearance of telavancin increased with

increasing ultrafiltration rate. However, the clearance of telavancin by CVVH has not been evaluated in a clinical study; thus, the clinical significance of this finding and use of CVVH to treat an overdose are unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, glycopeptide antibacterials, ATC code: J01XA03

Mechanism of action

Telavancin exerts concentration-dependent bactericidal activity against susceptible Gram-positive bacteria. Telavancin inhibits cell wall biosynthesis by binding to late-stage peptidoglycan precursors, including lipid II, which prevents polymerisation of the precursor into peptidoglycan and subsequent cross-linking events. Telavancin also binds to bacterial membranes and causes depolarisation of membrane potential and an increase in membrane permeability that results in inhibition of protein, RNA, and lipid synthesis.

Mechanism of resistance

S. aureus that exhibit high level resistance to glycopeptide antibacterial agents (GRSA) are not susceptible to telavancin. There is no known cross-resistance between telavancin and other non-glycopeptide classes of antibiotics.

Breakpoints

The minimum inhibitory concentration (MIC) breakpoints are as follows:

Pathogen	MIC (µg/ml)
S. aureus (including methicillin-resistant strains)	≤1

Microbiological susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Clinical efficacy and safety

Telavancin demonstrated efficacy against MSSA and MRSA in two randomised controlled studies in patients with nosocomial pneumonia, including ventilator-associated pneumonia, involving 751 patients who received telavancin. Despite *in vitro* susceptibility, there are insufficient clinical data to assess the potential for efficacy of telavancin in infections due to hGISA/GISA.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with VIBATIV in one or more subsets of the paediatric population in nosocomial pneumonia. See 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Telavancin exhibited linear pharmacokinetics at doses up to 15 mg/kg administered as a daily 60 minute intravenous infusion for 7 days in healthy volunteers. The mean (SD) maximum telavancin concentration (C_{max}) amounts to 108 (26) µg/ml at steady state at a once daily dose of 10 mg/kg infused over a period of 1 h (t_{max}) and then falls to a trough value of 8.55 (2.84) µg/ml (C_{24h}). Mean (SD) AUC_{0-24} amounts to 780 (125) µg.h/ml. Telavancin has a small volume of distribution. At a dose of 10 mg/kg, mean V_{ss} averaged between 133 (SD 24) ml/kg after multiple dosing, corresponding to a value of approximately 10 l for a 75 kg person. This data indicate that telavancin is not extensively

distributed. Telavancin is a low clearance drug with a mean (SD) CL of 13.1 (2.0) ml/hr/kg in subjects with normal renal function, corresponding to a total CL of approximately 1 l/hr in a 75 kg subject. In combination with the small V_{ss}, this results in a t½ of about 8 h.

Distribution
The apparent distribution volume of telavancin at steady-state in healthy adult subjects was approximately 133 ml/kg.

Human plasma protein binding is approximately 90%, primarily to serum albumin.

At a dose of 10 mg/kg for 3 consecutive days to healthy volunteers subjected to bronchoalveolar lavage, the concentration ratio in pulmonary epithelial lining fluid/plasma ranged from 0.050 and 0.121 over a period of 4 to 24 hours after start of infusion. Higher concentrations were observed in alveolar macrophages with ratios varying between 0.360 (at 4 h) and 6.67 (at 24 h). *In vitro* studies showed that telavancin retained full activity in the presence of pulmonary surfactant.

Biotransformation
In vitro studies have shown that CYP1A1, 1A2, 2B6, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5 and 4F12 are able to metabolise telavancin, resulting in hydroxylation at the 7, 8 and 9 position of the 2-(decylamino) ethyl side chain of telavancin.

In a mass balance study in male subjects using radiolabeled telavancin, 3 hydroxylated metabolites were identified with the predominant metabolite (THRX-651540) accounting for <10% of the radioactivity in urine and <2% of the radioactivity in plasma.

In healthy young adults, three hydroxylated metabolites were identified after infusion of telavancin. The AUC of the predominant metabolite accounted for approximately 2-3% of AUC of telavancin.

Elimination
Renal excretion is the major route of elimination for telavancin in humans. In healthy young adults, after infusion of radiolabeled telavancin, approximately 76% of the administered dose was recovered from urine and less than 1% of the dose was recovered from faeces (collected for up to 9 days), based on total radioactivity. Telavancin is mainly excreted unchanged accounting for approximately 82% of the total amount recovered over 48 hours in urine. The elimination half-life in subjects with normal renal function is approximately 8 hours.
Because renal excretion is the primary route of elimination, dosage adjustment is necessary in patients with a creatinine clearance of 30-50 ml/min (see section 4.2).

Special populations

Elderly
No clinically significant differences in pharmacokinetics of telavancin were observed between healthy elderly and healthy young subjects. Analysis of patient population pharmacokinetic data did not show a relevant effect of age on pharmacokinetics. Therefore, no dose adjustment is needed in elderly patients except in those with creatinine clearance of 30-50 ml/min (see sections 4.2 and 4.3).

Paediatric patients
The pharmacokinetics of telavancin in patients below 18 years of age have not been established (see section 4.2).

Gender
No clinically significant gender-related differences in telavancin pharmacokinetics have been observed. Therefore, no dosage adjustment is necessary based on gender.

Renal insufficiency
Pharmacokinetic parameters (mean (SD)) following a single dose administration of 7.5 mg/kg telavancin in volunteers with varying degrees of renal function are provided below.

	Degree of Renal Impairment				
	Normal	Mild	Moderate	Severe	ESRD[a]
CrCL (ml/min)[b]	93.8 (10.8)	64.1 (9.7)	40.3 (7.0)	21.0 (6.3)	NA
C_{max} (µg/ml)	70.6 (11.2)	65.9 (2.7)	65.8 (12.1)	71.8 (7.1)	52.1 (10.1)
AUC_{inf} (µg•h/ml)	560 (93)	633 (101)	721 (200)	1220 (120)	1010 (341)
$t_{½}$ (h)	6.90 (0.60)	9.6 (2.9)	10.6 (2.4)	14.5 (1.3)	11.8 (2.8)
CL (ml/h/kg)	13.7 (2.1)	12.1 (1.9)	11.1 (3.3)	6.18 (0.63)	8.18 (2.65)

[a] ESRD= End-stage renal disease maintained on haemodialysis
[b] Baseline mean creatinine clearance as calculated by Cockcroft-Gault equation

The effect of renal impairment on the pharmacokinetics of telavancin has been evaluated in 2 clinical pharmacology studies in healthy subjects with normal renal function and subjects with mild to severe renal impairment. Both studies consistently showed that the area under the curve (AUC) of telavancin, but not the maximum plasma concentration (C_{max}) increases with decreasing renal function. Changes in AUC only become clinically relevant in patients with moderate and severe renal impairment. Therefore, the same dose of 10 mg/kg/24 hr can be used in patients with normal renal function or mild renal impairment. To ensure a comparable exposure in patients with moderate renal impairment, the dose should be lowered to 7.5 mg/kg/24 hr.
Recommendations for dose adjustment can be found in section 4.2.

Hepatic impairment
Following administration of a single 10 mg/kg dose of telavancin, the pharmacokinetics of telavancin in subjects with moderate hepatic impairment (Child-Pugh class B) were similar to that observed in subjects with normal hepatic function. No adjustment of dosage is required for patients with mild to moderate degrees of hepatic impairment (see section 4.2). The pharmacokinetics of telavancin have not been evaluated in severe hepatic impairment (Child-Pugh class C).

5.3 Preclinical safety data
The telavancin medicinal product, which contains the excipient hydroxypropylbetadex(HP-ß-CD), induced adverse effects in animal studies at plasma concentrations that were in the same range as clinical exposure levels and with possible relevance to clinical use. The liver, kidney, macrophages and testis were identified as target organs of toxicity in animals.

In the liver, treatment for 13 weeks or longer resulted in reversible degeneration/necrosis of hepatocytes accompanied by elevations in serum AST and ALT in rats and dogs.

Effects on the kidney occurred after a minimum of 4 weeks of dosing and were a combination of renal tubular injury and tubular epithelial vacuolisation. The tubular injury was characterised by degeneration and necrosis of proximal tubular cells, and was associated with increases in BUN and creatinine that reach a maximum of 2 times the control values at the highest doses. The tubular injury was reversible, but not all animals had yet reached full recovery 4 weeks after the end of treatment.

Vacuolisation of tubular epithelium was a common observation in animals treated with the telavancin medicinal product and with the vehicle (HP-ß-CD). At higher doses or longer treatment durations, vacuolisation of the urothelium in the bladder also occurred. Vacuolisation was not associated with renal function impairment, but was not reversible after 4 weeks of recovery. Vacuolisation is considered to represent a cytoprotective event and is expected to reverse with the same half-life as the turnover time of the proximal tubular cells. The presence of hydroxypropylbetadex in the formulation at a ratio of 1:10 reduces the incidence and severity of the changes due to telavancin and attenuates the glycopeptides-like toxicity of telavancin.

Systemic macrophage hypertrophy and hyperplasia occurred in rats and dogs, in many organ systems that normally contain macrophages. The macrophages were shown to contain telavancin and HP-ß-CD.

Genotoxicity was addressed with a standard *in vitro* and *in vivo* test battery. The studies did not provide any evidence for a genotoxic potential of telavancin.

After 13 weeks of treatment, reversible seminiferous tubular degeneration was observed in the testis of rats. In studies on fertility in male rats, decreases in sperm motility and epididymal sperm counts as well as an increase in the frequency of abnormal sperm were demonstrated after 10 weeks of intravenous administration of telavancin. Male fertility was unaffected. In a second study, 6 weeks of dosing was associated with sloughed testicular germ cells in the epididymis, indicative of testicular injury, and effects upon sperm quality and quantity were observed. Both effects were reversible following an 8 week recovery period. The potential risk for humans is unknown (see section 4.6).

In rats and dogs vacuolisation of the epididymal tubular epithelium cells was also noted, and this finding did not show reversibility after a recovery period of 4 weeks. Vacuolisation is considered to be a cytoprotective event, which is not associated with functional impairment.

In embryo-fetal development studies malformations of digits and limbs were observed in rats, rabbits and minipigs. In the rat embryo-fetal development study dilatation of lateral ventricles of the brain was observed in the high dose group. An increase in the number of stillborn pups was observed in these pre- and post-natal studies (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex; the ratio of telavancin to hydroxypropylbetadex is 1:10 (w/w).
Mannitol (E421)
Sodium hydroxide (for pH adjustment) (E524)
Hydrochloric acid (for pH adjustment) (E507)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf life of powder as packaged for sale: 4 years

Shelf life of reconstituted concentrate: The reconstituted concentrate should be diluted immediately after preparation.

Shelf life of diluted product: Chemical and physical in use stability of the reconstituted solution

and the diluted solution in the infusion bag has been demonstrated for 24 hours under refrigeration (2-8°C).
From a microbiological point of view the product should be used immediately. If not used immediately, in use storage times are the responsibility of the user and should not be longer than 24 hours at 2-8°C.

6.4 Special precautions for storage

Powder as packed for sale
Store in a refrigerator (2–8°C). Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted or diluted medicinal product, see section 6.3.

6.5 Nature and contents of container
Type I clear glass vials with rubber stoppers and aluminium/plastic flip off cap.

Pack sizes:
1 vial of 30 ml with 250 mg telavancin
1 vial of 50 ml with 750 mg telavancin

6.6 Special precautions for disposal and other handling
The powder must be reconstituted and the resulting concentrate must then be immediately diluted further prior to use.

For single use only.

Preparation of the reconstituted concentrate (VIBATIV 250 mg vial)
The contents of the vial containing 250 mg telavancin must be reconstituted with 15 ml of either dextrose 50 mg/ml (5%) solution for injection, or water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to obtain a concentration of approximately 15 mg/ml (total volume of approximately 17 ml).
The following formula can be used to calculate the volume of reconstituted VIBATIV concentrate required to prepare a dose:
Telavancin dose (mg) = 10 mg/kg (or 7.5 mg/kg) x patient body weight (in kg)
Volume of reconstituted concentrate (ml) = Telavancin dose (mg)/15 (mg/ml)

Discard the vial if the vacuum does not pull the diluent into the vial.
Aseptic technique must be used to reconstitute VIBATIV. After addition of either dextrose 50 mg/ml (5%) solution for injection, or water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection, the contents of the vial are mixed by swirling gently to facilitate reconstitution.

Reconstitution time is not more than 5 minutes for the vial containing 250 mg.
Mixing is continued until the content of the vial is completely dissolved and is free of particulate matter by visual inspection.

Preparation of the reconstituted concentrate (VIBATIV 750 mg vial)
The contents of the vial containing 750 mg telavancin must be reconstituted with 45 ml of either dextrose 50 mg/ml (5%) solution for injection, or water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to obtain a concentration of approximately 15 mg/ml (total volume of approximately 50 ml).

The following formula can be used to calculate the volume of reconstituted VIBATIV concentrate required to prepare a dose:
Telavancin dose (mg) = 10 mg/kg (or 7.5 mg/kg) x patient body weight (in kg)
Volume of reconstituted concentrate (ml) = Telavancin dose (mg)/15 (mg/ml)
Discard the vial if the vacuum does not pull the diluent into the vial.

Aseptic technique must be used to reconstitute VIBATIV. After addition of either dextrose 50 mg/ml (5%) solution for injection, or water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection, the contents of the vial are mixed by swirling gently to facilitate reconstitution.

Reconstitution time is not more than 10 minutes for the vial containing 750 mg.
Mixing is continued until the content of the vial is completely dissolved and is free of particulate matter by visual inspection.

Appearance of reconstituted concentrate
A reconstituted concentrate of VIBATIV is a clear, colourless to pale pink solution. Foaming may occur during reconstitution but will dissipate upon standing.

Preparation of final diluted solution for infusion
Reconstituted concentrate must be further diluted prior to administration.
For doses of 150 to 800 mg, the appropriate volume of reconstituted concentrate must be further diluted in 100 to 250 ml prior to infusion. Doses less than 150 mg or greater than 800 mg should be further diluted in a volume resulting in a final solution of 0.6 to 8 mg/ml. Appropriate infusion solutions include: dextrose 50 mg/ml (5%) solution for injection, sodium chloride 9 mg/ml (0.9%) solution for injection or lactated Ringer's solution for injection. The dilution is to be made under aseptic conditions.

The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Disposal
Discard any unused solution.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Clinigen Healthcare Ltd
Pitcairn House,
Crown Square,
First Avenue
Burton-on-Trent
Staffordshire
DE14 2WW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)
EU/1/11/705/001
EU/1/11/705/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
2 September 2011

10. DATE OF REVISION OF THE TEXT
12 March 2014

Detailed information on this medicinal product is available on the website of the European Medicines Agency: **http://www.ema.europa.eu/**

PACKAGE LEAFLET: INFORMATION FOR THE USER

VIBATIV 250 mg powder for concentrate for solution for infusion
VIBATIV 750 mg powder for concentrate for solution for infusion
telavancin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk your doctor or pharmacist. This includes any possible side effects not litsted in this leaflet. See section 4.

What is in this leaflet:

1. What VIBATIV is and what it is used for
VIBATIV contains telavancin as active substance, which is an antibiotic of the glycopeptide group. VIBATIV is used to treat adult patients with infections of the lungs that have developed in the hospital, including patients on artificial ventilation, when these infections are known or suspected to be caused by bacteria called methicillin-resistant Staphylococcus aureus (MRSA).
It is only used when the bacteria that cause these infections can be killed with telavancin.
VIBATIV can only be used when other antibiotics are not suitable.

If you also have other bacteria that cause your infection, your doctor may prescribe other antibiotics in addition to VIBATIV.

2. What you need to know before you use VIBATIV

Do not use VIBATIV
- if you are allergic (hypersensitive) to telavancin or any of the other ingredients of VIBATIV (listed in section 6).
- If you suffer from severe kidney problems, or receive haemodialysis
- if you are pregnant

Take special care with VIBATIV

- if you have kidney problems. Your doctor may decide to reduce the dose of VIBATIV and monitor you more closely during treatment. Alternatively, your doctor may decide that this medicine is not suitable for you.
- if you are at greater risk of developing kidney disorders or if you are receiving other medicines that can affect your kidney. Your doctor will tell you if this is the case and may decide to monitor you more closely during treatment.

- if you experience skin reactions to the product. Your doctor may decide to adjust the rate of the infusion.
- if you are allergic to antibiotics such as vancomycin. Tell your doctor immediately if this is the case.
- if you are suffering from heart disorders. Tell your doctor immediately if this is the case.
- if you notice a change in your hearing. Tell your doctor immediately if this is the case. Your doctor may monitor your hearing during treatment. Ringing in the ears and deafness are possible side effects.
- While antibiotics including VIBATIV fight certain bacteria, other bacteria and fungi may continue to grow. This is called overgrowth. Your doctor will monitor you for any potential infections and treat you if necessary.
- if you develop diarrhoea during or shortly after your treatment, tell your doctor immediately. Do not take any diarrhoea medicine without first checking with your doctor.
- if you are suffering from more than one infection. Your doctor will treat you as necessary.

Use in children
Telavancin is not to be used in children or adolescents under 18 years of age.

Other medicines and VIBATIV
Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Telavancin may interfere with some laboratory tests that measure how well your blood is clotting. The test results can suggest poor blood clotting when, in fact, there is no problem. Tell your doctor that you are receiving VIBATIV.

Telavancin may interfere with some laboratory tests that measure proteins in the urine. Tell your doctor that you are receiving VIBATIV.

Pregnancy and breast-feeding
Telavancin must not be given to pregnant women. Tell your doctor if you are pregnant, think you may be pregnant, or are trying to become pregnant. You have to use effective contraception during treatment with VIBATIV.

It is not known if telavancin passes into breast milk in humans. Ask your doctor for advice before breastfeeding your baby.

Driving and using machines
VIBATIV may cause side effects, such as dizziness, sleepiness, confusion or blurred vision that can have an influence on the ability to drive or operate machinery.

Important information about some of the ingredients of VIBATIV
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium-free’.

3. How to use VIBATIV
VIBATIV will be given to you by a doctor or a nurse.
The dose given will depend on how much you weigh. The dose for adults (18 years and older) is 10 milligrams (mg) for every kilogram (kg) of body weight, given once a day. This dose is given as an infusion (drip into a vein) over a period of about 60 minutes. If your kidneys do not work well, the dose may be reduced.

A course of treatment usually lasts for 7 to 21 days. Your doctor will decide how long you should be treated.

If you use more VIBATIV than you should
If you are given more VIBATIV than you should receive, the chance of experiencing the following side effects increases: disturbed taste, nausea (feeling sick), vomiting, reactions at the site of the infusion, headache, rash, skin flushing of the upper body. If this happens, the infusion of telavancin will be stopped and the doctor will check the functioning of your kidneys.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, VIBATIV can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
Not known: frequency cannot be estimated from the available data

VIBATIV may cause the following side effects:

Very common
- taste disturbance
- nausea (feeling sick)

Common
- fungal infections
- sleeplessness
- headache, dizziness
- constipation, diarrhoea; vomiting
- raised blood levels of liver enzymes
- itching, rash
- kidney disorder, abnormal kidney function tests, foamy urine
- tiredness, chills

Uncommon
- intestinal bacterial infection; urinary tract infection
- anaemia, changes in white blood cell counts; changes in blood platelet counts
- allergic reactions
- decreased appetite; changes in blood levels of glucose; changes in blood levels of potassium and magnesium
- restlessness; anxiety; confusion; depression
- loss of taste, migraine, abnormal touch sensation, smell disturbance, sleepiness, trembling,
- eye irritation; blurred vision
- ringing in your ears
- chest pain; heart failure; abnormal heart rhythm or heart beat
- flushing; high or low blood pressure; inflammation of a vein
- breathlessness, hiccups, nasal congestion, sore throat
- abdominal pain; dry mouth; indigestion, bloating; numbness of the mouth
- liver inflammation
- skin redness; swelling of face; sweating, hives
- joint pain; back pain; muscle cramp; muscle pain
- painful urination; blood in urine; low urine output, frequent urination; abnormal urine odour

- lack of energy; irritation at infusion site; feeling unwell; chest discomfort; accumulation of fluid in the lower legs; pain; fever; skin flushing of upper body
- abnormal blood clotting tests

Rare
- deafness

Not known
- severe allergic reactions (anaphylaxis). The first signs of a severe allergic reaction may include swelling of the skin, face and/or throat and/or difficulty breathing. If these symptoms occur you must inform your doctor or nurse immediately

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via
ADR Reporting
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VIBATIV
Keep out of the reach and sight of children.

Do not use VIBATIV after the expiry date that is stated on the label and carton after EXP: The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Keep the vial in the outer carton to protect the product from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What VIBATIV contains
Each vial contains 250 mg or 750 mg telavancin (as hydrochloride). After reconstitution, each ml of concentrated solution contains 15 mg of telavancin. The other ingredients are hydroxypropylbetadex, mannitol (E421), sodium hydroxide (E524) and hydrochloric acid (E507) (for pH adjustment).

What VIBATIV looks like and contents of the pack
VIBATIV powder for concentrate for solution for infusion is provided as a 30 ml or 50 ml clear glass vial with rubber stopper, with an aluminium closure with plastic flip-off caps. The vial contains a white to pale pink powder.

Pack sizes:
1 vial of 30 ml with 250 mg telavancin
1 vial of 50 ml with 750 mg telavancin

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Clinigen Healthcare Ltd
Pitcairn House,
Crown Square,
First Avenue
Burton-on-Trent
Staffordshire
DE14 2WW
United Kingdom

Manufacturer:

Biotec Services International Limited
Biotec House
Central Park, Western Avenue
Bridgend Industrial Estate
Bridgend, CF31 3RT
United Kingdom

This leaflet was last approved in March 2014.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: **http://www.ema.europa.eu**

The following information is intended for medical or healthcare professionals only:

Method of administration
VIBATIV must be reconstituted and then further diluted prior to administration by intravenous infusion through a dedicated line or through a Y-site over a 60 minute period. Bolus injections must not be administered.

The following formula can be used to calculate the volume of reconstituted VIBATIV concentrate required to prepare a dose:

Telavancin dose (mg) = 10 mg/kg (or 7.5 mg/kg) x patient body weight (in kg)

Volume of reconstituted concentrate (ml) = Telavancin dose (mg)/15 (mg/ml)

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Shelf life of reconstituted concentrate: The reconstituted concentrate should be diluted immediately after preparation.

Shelf life of diluted product: Chemical and physical in use stability of the reconstituted solution and the diluted solution in the infusion bag has been demonstrated for 24 hours under refrigeration (2-8°C). From a microbiological point of view the product should be used immediately. If not used

immediately, in use storage times are the responsibility of the user and should not be longer than 24 hours at 2-8°C.

Special precautions for disposal and other handling
The powder must be reconstituted and the resulting concentrate must then be immediately diluted further prior to use.

Preparation of the reconstituted concentrate (VIBATIV 250 mg vial)
The contents of the vial containing 250 mg telavancin must be reconstituted with 15 ml of either dextrose 50 mg/ml (5%) solution for injection, or water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to obtain a concentration of approximately 15 mg/ml (total volume of approximately 17 ml).

Preparation of the reconstituted concentrate (VIBATIV 750 mg vial)
The contents of the vial containing 750 mg telavancin must be reconstituted with 45 ml of either dextrose 50 mg/ml (5%) solution for injection, or water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to obtain a concentration of approximately 15 mg/ml (total volume of approximately 50 ml).

Discard the vial if the vacuum does not pull the diluent into the vial.

Aseptic technique must be used to reconstitute VIBATIV. After addition of either dextrose 50 mg/ml (5%) solution for injection, or water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection, the contents of the vial are mixed by swirling gently to facilitate reconstitution.

Reconstitution time is not more than 5 minutes for the vial containing 250 mg.
Reconstitution time is not more than 10 minutes for the vial containing 750 mg.
Mixing is continued until the content of the vial is completely dissolved and is free of particulate matter by visual inspection.

Appearance of reconstituted concentrate
A reconstituted concentrate of VIBATIV is a clear, colourless to pale pink solution. Foaming may occur during reconstitution but will dissipate upon standing.

Preparation of final diluted solution for infusion
Reconstituted concentrate must be further diluted prior to administration.
For doses of 150 to 800 mg, the appropriate volume of reconstituted concentrate must be further diluted in 100 to 250 ml prior to infusion. Doses less than 150 mg or greater than 800 mg should be further diluted in a volume resulting in a final solution of 0.6 to 8 mg/ml. Appropriate infusion solutions include: dextrose 50 mg/ml (5%) solution for injection, sodium chloride 9 mg/ml (0.9%) solution for injection or lactated Ringer's solution for injection. The dilution is to be made under aseptic conditions.
The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Disposal
For single use only. Discard any unused solution.

Any unused product or waste material should be disposed of in accordance with local requirements. or in accordance with local requirements.


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